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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,692	01/16/2002	Darrell H. Carney	3033.1002-004	6715
21005	7590	04/06/2004	EXAMINER	
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.			DEBERRY, REGINA M	
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P.O. BOX 9133			PAPER NUMBER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/050,692	Applicant(s) CARNEY ET AL.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 11-19 and 41-46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 11-19 and 41-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/25/03</u> . | 6) <input type="checkbox"/> Other: _____ |

Status of Application, Amendments and/or Claims

The amendment filed 05 January 2004 has been entered in full. Claims 1-5, 11-19 and 41-46 are under examination.

The Declaration of Darrell H. Carney under 37 CFR 1.132 filed 05 January 2004 has been entered.

The application now complies with the requirements of 37 CFR 1.821-1.825.

Applicants have stated that a Supplemental Information Disclosure Statement (IDS) was filed on 25 July 2003. Applicants have requested entry and consideration of the IDS. The information disclosure statement, filed 25 July 2003, was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 5, 11, 12 and 35-43 are under 35 U.S.C. 112, second paragraph, as set forth at pages 2-3 of the previous Office Action (20 August 2003) is *withdrawn* in view of the amendment (05 January 2004).

Double Patenting

Claims 1-5, 11-19, 41-46 remain provisionally rejected under 35 U.S.C. 101 (statutory type 35 U.S.C. 101 double patenting rejection) as claiming the same invention as that of claims 1-5, 11-16, 35-43 of copending Application No. 09/909122. The basis for this rejection is set forth at page 12 of the previous Office Action (20 August 2003).

Applicants have stated that if appropriate, claims 1-5, 11-19 and 41-46 will be canceled when there is an indication of allowable subject matter.

The rejection is maintained for reasons of record but the Examiner has acknowledge Applicants' intention to cancel.

Claim Rejections - 35 USC § 102(b)

Claims 1-5, 11, 12, 19 and 41-43 remain rejected under 35 U.S.C. 102(b) as being anticipated by Simmons *et al.*, "Acceleration of Rat Femoral Fracture Healing by a Synthetic Thrombin Peptide", meeting held 20 November 1998 (IDS#AS3 submitted by Applicant, Paper No. 8). The basis for this rejection is set forth at page 10 of the previous Office Action (20 August 2003).

Applicants state that claims 1-5, 11, 12, 19 and 41-43 relate to the use of NPAR agonists, including TP508 (SEQ ID NO:5), in stimulating bone growth at a site in need of osteoinduction or in need of a bone graft. Applicants state that osteoinduction is defined in the subject application at page 3, lines 20-21 as a site at which bone growth would not occur if the site were left untreated. Such sites in need of osteoinduction include segmental bone gaps, bone voids and at non-union fractures. The healing

process (bone regeneration) at such a site does not occur without osteoinduction or bone grafting.

Applicants state that Example 2 of the specification teaches that an injury resulting in a segmented gap did not heal when it was left untreated; bone regeneration (osteoinduction) did not occur at the segmented gap. When the site was treated with TP508, osteoinduction was induced where it did not occur without TP508. Applicants argue that Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the progression of rat femoral fracture healing. Applicants maintain that healing of this fracture (bone regeneration) was occurring prior to TP508 treatment, indicating that treatment (including bone grafting and osteoinduction) was not required for normal bone growth. Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the rate of normal fracture healing in a fracture that normally heals without treatment. Applicants maintain that Simmons *et al.* do not teach or suggest the use of TP508 for stimulating bone formation at a site in need of osteoinduction or bone grafting, i.e. at a site where bone growth would not occur if the site was left untreated. Applicants assert that claims 1-5, 11, 12, 19 and 41-43 are not anticipated by the Simmons *et al.* reference.

Applicants' arguments have been fully considered but are not deemed persuasive because the term "osteoinduction" as defined by the instant specification is not the accepted art definition of osteoinduction. The Examiner has provided a reference to support the argument. Albrektsson *et al.* (Abstract, European Spine Journal 2001) define osteoinduction as the process by which osteogenesis is induced. It

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is a phenomenon regularly seen *in any type of bone healing process*. Albrektsson *et al.* state that in a bone healing situation, such as a fracture, the majority of bone healing is dependent on osteoinduction. Applicant cannot define a term of art that is repugnant to its accepted meaning in the art. Please MPEP 608.01(o). Simmons *et al.* teach methods of administering TP508 to stimulate bone growth at a site in rats in need of bone repair due to fracture. Furthermore, a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Simmons *et al.* and the instant specification both teach the administration of TP508.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 103(a)

Claims 16-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Simmons *et al.*, "Acceleration of Rat Femoral Fracture Healing by a Synthetic Thrombin Peptide", meeting held 20 November 1998 (IDS#AS3 submitted by Applicant, Paper No. 8) in view of in view of Schmitz, US Patent No. 4,637,931. The basis for this rejection is set forth at pages 10-12 of the previous Office Action (20 August 2003).

Applicants state that Schmitz does not teach or suggest the use of pharmaceutical compositions comprising an NPAR agonist, such as TP508 (SEQ ID NO:5) in stimulating bone growth at a site in need of osteoinduction and thus the reference does not cure the deficiencies of the Simmons *et al.* reference. Applicants

state that the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references.

Applicants' arguments have been fully considered but are not deemed persuasive. The MPEP 2143 states (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Contrary to Applicants' assertion, the Examiner used the teachings of the prior art and the knowledge available to one of ordinary skill in the art, not the instant specification to piece together the combination of references to establish a prima facie case of obviousness. Furthermore, the Examiner discussed the motivation and reasonable expectation of success using the prior, not Applicants' disclosure. The Examiner has already discussed the reasons why claims 1-5, 11, 12, 19 and 41-43 are anticipated by the Simmons *et al.* (reference teaches pharmaceutical compositions comprising TP508). As was stated in the last Office Action, Simmons *et al.* do not teach

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implantable osteoconductive matrix comprising polylactic acid/polyglycolic acid homopolymer (PLA/PGA) or copolymer. As was stated in the last Office Action, Schmitz teaches methods comprising implanting at the site of the broken osseous tissue a therapeutically effective amount of a composition comprising decalcified freeze dried bone incorporated into a biodegradable polymeric matrix of PLA/PGA. Schmitz teaches that PGA and PLA have demonstrated an accelerate rate of osseous wound healing and produce only a slight inflammatory response. Schmitz teaches that PLA and PGA eliminates the need for a second surgical procedure in the host, biodegrades without forming toxic metabolites, has the ability to act as a trestle for bony ingrowth and may also possess osteogenic potential. Based on the discussion, it would be obvious to one skilled in the art to combine the teachings of Simmons *et al.* and Schmitz to make the instant invention.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

Claims 1-5, 11-19, 41-46 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated

thrombin receptor wherein the agonist is a thrombin derivative comprising a polypeptide 23 amino acids in length and is represented by the following structure

Arg-Gly-Asp-Ala-**R** wherein **R** is a serine esterase conserved sequence and wherein Asp-Ala of said structure comprise the first two amino acids of the serine esterase conserved sequence **OR**

an agonist comprising SEQ ID NO:5 **OR**

an agonist comprising SEQ ID NO:6,

does not reasonably provide enablement for:

a method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pages 5-8 of the previous Office Action (20 August 2003).

Applicants' arguments have been fully considered and are deemed partly persuasive. Applicants cite pages in the specification for support regarding the activity of NPAR agonists and methods for identifying, screening and making NPAR agonists. Applicants also cite US Patent Nos. 5,352,664 and 5,500,412 for support. Applicants state that specific examples of NPAR agonists provided in the specification include thrombin peptide derivatives comprising a polypeptide represented by the structural formula Asp-Ala-R, wherein R is a serine esterase conserved sequence, such as the

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background of the instant patent does not teach agonist (stimulatory peptides) of non-proteolytically activated thrombin receptor modified to an unlimited extent relative to those exemplified. The instant claims, however encompass any type of agonist of the non-proteolytically activated thrombin receptor, functional equivalent, fragments or substitutions thereof. Furthermore, Example 4 of US Patent No. 5,352,664 teaches that peptide 508-530 (23 amino acid sequence comprising AGYKPDEGKRGDACEGDSGGPFV) generated mitogenic signals through its interaction with the thrombin receptor. However, peptide 519-530 (12 amino acid sequence comprising DACEGDSGGPFV) and peptide 517-520 (4 amino acid sequence comprising RGDA) did not exhibit mitogenic activity as great as peptide 508-530 (Figure 6) and took a much greater concentration to compete with alpha-thrombin binding (Table 1). Thus, US Patent No. 5,352,664 teaches a specific domain (thrombin receptor binding domain), conserved sequences (serine esterase conserved sequence) and a minimum amino acid length (23 amino acids) of stimulatory agonist of the non-proteolytically activated receptor. Lastly, the allowed claims of both US Patent No. 5,352,664 and US Patent No. 5,500,412 recite specific claim language regarding sequence and amino acid length of stimulatory thrombin derivatives. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 1-4 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pages 8-9 of the previous Office Action (20 August 2003).

Applicants state that detailed characteristics for the NPAR agonists are recited in the rejected claims. Applicants state that the specification teaches that NPAR agonists are compounds which stimulate or activate NPAR and that methods for assaying for NPAR activation are disclosed in the specification and the recited patents. Applicants conclude by stating that the knowledge and level of skill in the field is high and a person skilled in the art would recognize from the disclosed characteristic that Applicants were in possession of the claimed genus of NPAR agonists at the time the present application was filed.

Applicant's arguments have been fully considered but are not deemed persuasive because methods for identifying and screening for NPAR agonists do not correlate to disclosure of NPAR agonists. The genus of "agonist of the non-proteolytically activated receptor" is being claimed by function alone. There is no structural element correlative with the function, nor is there any indication that Applicant is in possession of any agonist of the non-proteolytically activated receptor. Furthermore, the instant species of agonist are not representative of the broad genus being claimed because the recitation of "an agonist of the non-proteolytically activated receptor", broadly encompasses lipids, protein, chemical analogs, polynucleotides, etc. None of these sequences meet the written description provision of 35 USC 112, first paragraph. Thus, there is insufficient descriptive support for the instant genus. The

instant method requires the use of undisclosed agonist or functional analogs. The specification does not demonstrate possession of the instant process steps which require the use of undisclosed compounds. The specification provides insufficient written description to support the genus encompassed by the claim. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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3/23/04


YVONNE EYLER, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600